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ORIGINAL RESEARCH

NT-proBNP and All-Cause and Cardiovascular Mortality in US Adults: A Prospective Cohort Study

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BACKGROUND: NT-proBNP (N-terminal pro-B-type natriuretic peptide) is strongly associated with mortality in patients with heart failure. Prior studies, primarily in middle-aged and older populations, have suggested that NT-proBNP has prognostic value in ambulatory adults.

METHODS AND RESULTS: We conducted a prospective cohort analysis of adults, aged ≥20 years, in the nationally representative 1999 to 2004 National Health and Nutrition Examination Survey, to characterize the association of NT-proBNP with mortality in the general US adult population overall and by age, race and ethnicity, and body mass index. We used Cox regression to characterize associations of NT-proBNP with all-cause and cardiovascular disease (CVD) mortality through 2019, adjusting for demographics and cardiovascular risk factors. We included 10 645 individuals (mean age, 45.7 years; 50.8% women; 72.8% White adults; 8.5% with a self-reported history of CVD). There were 3155 deaths (1009 CVD-related) over a median 17.3 years of follow-up. Among individuals without prior CVD, elevated NT-proBNP (≥75th percentile [81.5 pg/mL] versus <25th percentile [20.5 pg/mL]) was associated with a significantly higher risk of all-cause (hazard ratio [HR], 1.67 [95% CI, 1.39–2.00]) and CVD mortality (HR, 2.87 [95% CI, 1.61–5.11]). Associations of NT-proBNP with all-cause and CVD mortality were generally similar across subgroups defined by age, sex, race and ethnicity, or body mass index (all *P* interaction >0.05).

CONCLUSIONS: In a representative sample of the US adult population, NT-proBNP was an important independent risk factor for all-cause and CVD mortality. NT-proBNP may be useful for monitoring risk in the general adult population.

Key Words: biomarkers ■ brain ■ cardiovascular disease ■ epidemiology ■ mortality ■ natriuretic peptide ■ prevention

NT-proBNP (N-terminal pro-B-type natriuretic peptide) is a stable amino acid fragment released from ventricular cardiac myocytes in response to stretch.[1,2] NT-proBNP is routinely used in the clinical management of congestive heart failure.[1–3] NT-proBNP levels reflect a variety of cardiometabolic processes[1] and may have a use for monitoring cardiovascular risk and guiding primary prevention of cardiovascular disease (CVD). Several studies in middle-aged and older ambulatory populations have demonstrated that NT-proBNP is associated with an increased risk of mortality and CVD, especially heart failure.[4–12] However, there have been no prior studies of NT-proBNP and mortality in a nationally representative sample of US adults of all ages.

Major demographic differences in NT-proBNP have raised questions about its equivalence and interpretation across important population subgroups. In older adults, elevated NT-proBNP levels have been shown to be independently associated with increased risk of cardiovascular and all-cause mortality.[5] Less data

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CLINICAL PERSPECTIVE

What Is New?

- Nationally representative data on the relation of NT-proBNP (N-terminal pro-B-type natriuretic peptide) with mortality among US adults are scant.
- An important proportion of US adults without a history of cardiovascular disease have elevated NT-proBNP.
- Among adults without a history of cardiovascular disease, increasing levels of NT-proBNP were significantly associated with all-cause and cardiovascular mortality, similarly across subgroups defined by age, sex, race and ethnicity, or body mass index.

What Are the Clinical Implications?

- Our findings highlight the importance of NT-proBNP for monitoring risk in the general adult population.

Nonstandard Abbreviations and Acronyms

NHANES	National Health and Nutrition Examination Survey

are available in diverse samples of adults as young as 20 years of age. There are major differences in NT-proBNP by race and ethnicity, with significantly lower NT-proBNP levels among Black individuals compared with White individuals.[13–15] Limited information is available on Hispanic populations, although a prior study demonstrated that Hispanic adults have NT-proBNP levels that are intermediate between those of Black and White individuals.[16] NT-proBNP is profoundly affected by adiposity, with lower levels of NT-proBNP observed among individuals with higher body mass index compared with those without excess adiposity[17,18]; the implications of these differences for the use of NT-proBNP for monitoring risk in the general adult population remain unclear.

We undertook this study to assess the utility of NT-proBNP as an independent risk factor for all-cause and cardiovascular mortality in the general US adult population and important population subgroups. We used data from adults, aged ≥20 years, who participated in the 1999 to 2004 National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of US adults. We examined potential differences in the association of NT-proBNP with mortality by age, race and ethnicity, and adiposity levels.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

The NHANES is a nationally representative sample of the noninstitutionalized, civilian population in the United States. We measured NT-proBNP in stored serum samples from all individuals with available blood in NHANES 1999 to 2004. There was a total of 12 298 participants, aged ≥20 years, in NHANES 1999 to 2004 with available specimen and data on mortality linkage. Of this group, we excluded pregnant women (n=663) and those with missing data on the relevant covariates (n=990). Our analytic sample included 10 645 participants, including 1256 with self-reported CVD.

Informed consent was obtained from all participants. The NHANES protocols and the measurement of NT-proBNP in stored specimen were approved by the National Center for Health Statistics ethics review board.

NT-proBNP Measurement

We measured NT-proBNP in stored serum samples at the University of Maryland School of Medicine (Baltimore, MD) between 2018 and 2020. NT-proBNP was measured by electrochemiluminescence immunoassay (Roche Diagnostics Corp) on a Cobas e601 analyzer (Elecsys; Roche Diagnostics, Indianapolis, IN). The NT-proBNP assay had a coefficient of variation between 2.7% and 3.1%. The upper and lower limits of detection of NT-proBNP were 35 000 and 5 pg/mL, respectively. The values of NT-proBNP that were below the limit of detection were recoded to limit of detection/$\sqrt{2}$, and the values above the upper limit of detection were recoded to the upper limit of detection.[19]

Outcome: Mortality

The vital status of participants was ascertained through a probabilistic match between NHANES personal identifiers and linkage to death certificates from the National Death Index through December 31, 2019.[20] Cardiovascular mortality and other causes of death were identified based on the underlying cause of death based on *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes I00 to I99.

Other Variables of Interest

Demographic and lifestyle information, including information on smoking, alcohol, and physical activity, was self-reported and collected using a computer-assisted personal interview system.

Height and weight were measured at the mobile examination center and were used to calculate body mass index (BMI) in kg/m^2. Hypertension was defined using a mean systolic blood pressure ≥140 mm Hg, mean diastolic blood pressure ≥90 mm Hg, or self-reported history of diagnosis by health care provider. Hemoglobin A_{1C} was measured by high-performance liquid chromatography on the Primus CLC330 and Primus CLC385 instruments (Primus, Kansas City, MO). We defined diabetes as a hemoglobin A_{1C} ≥6.5% or self-reported history of diagnosis by health care provider. Total cholesterol was measured using an enzymatic method. Hypercholesterolemia was defined as total cholesterol ≥240 mg/dL or self-reported lipid-lowering medication use.

Participants self-reported a history of CVD (congestive heart failure, coronary heart disease, angina, heart attack, or stroke) diagnosed by a health care provider. Chronic kidney disease was defined by an estimated glomerular filtration rate <60 mL/min per 1.73 m^2 based on the new Chronic Kidney Disease Epidemiology Collaboration equation (using creatinine and cystatin C)[21] or 1-time urine albumin/creatinine ratio ≥30 mg/g.

Statistical Analysis

We accounted for the complex survey design and used the relevant survey weights in all analyses to generate estimates generalizable to the 1999 to 2004 US adult population. SEs for all estimates were obtained using Taylor series linearization. We summarized the baseline characteristics of participants across quartiles of NT-proBNP among those without prior CVD. Participants with a self-reported history of CVD were considered separately, regardless of their NT-proBNP level. We assessed differences using χ^2 tests for categorical variables and ANOVA or Kruskal-Wallis test for continuous variables. We generated weighted histograms to show the distributions of NT-proBNP in the overall population and in subgroups defined by age, sex, race and ethnicity, and BMI.

We calculated the prevalence of elevated NT-proBNP using clinically relevant cut points (≥100, ≥125, ≥300, and ≥450 pg/mL)[22,23] and estimated the corresponding number of US adults in these categories by applying these proportions to the 2003 to 2004 population totals.[24]

We calculated rates (per 1000 person-years) of all-cause and cardiovascular mortality using Poisson regression according to quartiles of NT-proBNP, with prevalent self-reported CVD considered as a separate category. We used Kaplan-Meier analyses and Cox regression models to assess the associations of baseline NT-proBNP (in quartiles) and self-reported CVD with all-cause and cardiovascular mortality. Adjusted models included age, sex, race and ethnicity, education, alcohol use, smoking status, physical activity, BMI, hypertension, diabetes, hypercholesterolemia, and estimated glomerular filtration rate. We checked the proportional hazard assumption using log-log plots and scaled Schoenfeld residuals.

We modeled the continuous associations of NT-proBNP with all-cause and cardiovascular mortality using restricted cubic splines (4 knots, at 5, 35, 65, and 95 percentiles) in people with and without a history of CVD. The splines were reported on an arithmetic scale, as it is important to show risk associations using the real (untransformed) values, which are more clinically relevant. To deal with the right-skewed nature of the data, the high values were binned, and the plots were truncated.

In adults without CVD, we conducted sensitivity analyses using binary categories of NT-proBNP defined on the basis of established cut points (≥100, ≥125, ≥300, and ≥450 pg/mL). We conducted analyses stratified by age, sex, race and ethnicity, and BMI categories (<25, 25–<30, and ≥30 kg/m^2) and tested for multiplicative effect modification by these variables.

Stata version 17.0 (College Station, TX) was used for all analyses. A 2-sided P<0.05 was considered statistically significant.

RESULTS

Characteristics of the Study Participants

Among the 10 645 study participants weighted to the general US adult population (mean age, 45.7 years [median age, 44 years {25th percentile–75th percentile, 33.0–57.0 years}]; 50.8% women; and 72.8% White adults), 8.5% had a self-reported history of CVD. The median (25th percentile–75th percentile) NT-proBNP level among people without a history of CVD was 42.4 pg/mL (20.9–82.5 pg/mL). In people with a history of CVD, the median (25th percentile–75th percentile) NT-proBNP was 168.5 pg/mL (62.2–438.2 pg/mL).

Among individuals without CVD, those in higher quartiles of NT-proBNP were older, and were more likely to be White race, women, and physically inactive, and have hypertension, diabetes, dyslipidemia, or chronic kidney disease (Table 1). Individuals with a history of CVD were substantially older, less likely to be physically active, had a higher BMI, and were more likely to have diabetes, hypertension, hypercholesterolemia, or chronic kidney disease compared with individuals in the highest quartile of NT-proBNP (Table 1). Figure S1 shows the extent of the variation in the distribution of NT-proBNP by age, sex, BMI, and race and ethnicity.

The proportions of US adults without a history of CVD who had NT-proBNP ≥100, ≥125, ≥300, and ≥450 pg/mL were 19.3% (SE, 0.6%), 14.3% (SE, 0.5%), 4.0% (SE, 0.2%), and 2.4% (SE, 0.2%), respectively (Table 2). Overall, 29.9 million adults had NT-proBNP

Table 1. Characteristics of US Adults, Aged ≥20 Years, According to Quartiles of NT-proBNP and History of CVD, NHANES 1999 to 2004

Characteristic	No history of CVD				History of CVD
NT-proBNP quartile	Quartile 1 (<20.91 pg/mL)	Quartile 2 (20.91 to <42.44 pg/mL)	Quartile 3 (42.44 to <82.45 pg/mL)	Quartile 4 (≥82.45 pg/mL)	Any
Unweighted No.	2250	2172	2157	2810	1256
NT-proBNP, median (p25–p75), pg/mL	12.4 (7.7–16.3)	30.1 (25.3–36.0)	58.6 (49.7–68.6)	138.6 (102.4–218.7)	168.5 (62.2–438.2)
Age, mean (SE), y	36.7 (0.4)	40.2 (0.3)	44.7 (0.4)	55.7 (0.4)	63.6 (0.6)
Female sex, % (SE)	22.5 (0.9)	43.8 (1.1)	64.3 (1.3)	73.8 (0.7)	47.6 (1.8)
Race, % (SE)					
Non-Hispanic White race and ethnicity	59.4 (2.0)	71.0 (1.8)	76.9 (1.5)	81.1 (1.9)	80.3 (1.7)
Non-Hispanic Black race and ethnicity	16.2 (1.5)	11.1 (1.0)	7.7 (0.8)	7.3 (1.0)	9.8 (1.3)
Mexican American ethnicity	10.5 (1.2)	8.2 (1.0)	6.0 (0.8)	4.0 (0.7)	3.0 (0.7)
Other Hispanic ethnicity	13.9 (1.9)	9.7 (1.4)	9.4 (1.1)	7.6 (1.4)	6.9 (1.4)
Education, % (SE)					
Less than high school	19.5 (1.0)	17.7 (1.0)	15.8 (1.0)	20.5 (1.0)	32.4 (2.0)
High school	24.9 (1.5)	23.6 (1.1)	27.6 (1.2)	28.0 (1.1)	28.2 (1.7)
Associate degree	30.8 (1.2)	33.4 (1.3)	29.2 (1.2)	28.0 (1.0)	25.1 (1.4)
College graduate and above	24.8 (1.6)	25.3 (1.6)	27.4 (1.5)	23.5 (1.6)	14.4 (1.1)
Smoking, % (SE)					
Never	53.1 (1.7)	51.7 (1.6)	50.7 (1.5)	47.9 (1.1)	37.1 (2.0)
Former	19.5 (1.0)	21.2 (1.3)	25.1 (1.3)	28.7 (1.1)	41.3 (1.6)
Current	27.5 (1.4)	27.0 (1.4)	24.2 (1.2)	23.3 (1.0)	21.5 (1.7)
Drinking, % (SE)					
Never	10.0 (1.3)	10.3 (1.2)	12.4 (1.4)	15.8 (1.4)	15.9 (1.6)
Former	12.8 (1.1)	12.9 (1.0)	15.2 (1.2)	20.5 (1.1)	33.8 (1.9)
Moderate	34.4 (1.6)	35.8 (1.7)	34.1 (1.5)	33.6 (1.6)	33.8 (2.1)
Heavy	42.9 (1.6)	41.0 (1.5)	38.3 (1.3)	30.1 (1.5)	16.5 (1.5)
Body mass index, mean (SE), kg/m^2	28.4 (0.1)	28.1 (0.2)	27.7 (0.2)	27.7 (0.2)	29.4 (0.3)
Physically active, % (SE)*	66.5 (1.6)	66.8 (1.6)	66.9 (1.5)	60.1 (1.4)	49.1 (1.8)
Diabetes, % (SE)					
No diabetes	76.7 (1.3)	79.4 (1.2)	78.9 (1.1)	71.0 (1.4)	49.2 (1.6)
Prediabetes	17.4 (1.1)	14.4 (0.9)	14.5 (1.0)	19.6 (1.1)	25.7 (1.7)
Diabetes	5.9 (0.8)	6.2 (0.7)	6.5 (0.5)	9.4 (0.6)	25.1 (1.6)
Hypertension, % (SE)	25.0 (1.1)	23.4 (1.2)	30.4 (1.1)	48.1 (1.3)	70.8 (2.2)
Hypercholesterolemia, % (SE)	30.0 (1.1)	29.3 (1.4)	32.2 (1.1)	38.6 (1.3)	62.3 (1.9)
Chronic kidney disease, % (SE)	5.2 (0.6)	5.4 (0.5)	8.1 (0.6)	19.5 (1.0)	33.2 (1.6)

CVD indicates cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; NT-proBNP, N-terminal pro-B-type natriuretic peptide; p25, 25th percentile; p75, 75th percentile; and SE, standrad error.

*Physically active was defined as physical activity levels ≥500 metabolic equivalent/min per week. All *P* values for comparisons across NT-proBNP levels were <0.001.

≥125 pg/mL, and 7.4 million adults had NT-proBNP levels of ≥300 pg/mL.

NT-proBNP and All-Cause and Cardiovascular Mortality

Over a median follow-up of 17.3 years, there were 3155 deaths (1009 cardiovascular-related). Among individuals without a history of CVD, people in the highest quartile of NT-proBNP had the highest rates of all-cause or cardiovascular mortality (Table 3). This elevated risk persisted after adjustment for demographic and cardiovascular risk factors; those people in the highest NT-proBNP quartile (≥82.5 pg/mL) had a significantly higher risk of all-cause (hazard ratio [HR], 1.67 [95% CI, 1.39–2.00]) and cardiovascular mortality (HR, 2.87 [95% CI, 1.61–5.11]) compared with people in

Table 2. Prevalence of Elevated NT-proBNP and Number (in Millions) of US Adults, Aged ≥20 Years, Without a History of CVD Overall and by Age Group, NHANES 1999 to 2004

Variable	Overall, % (SE)	Age group, y			No. of US adults (in millions)*
		<40, % (SE)	40 to <65, % (SE)	≥65, % (SE)	
NT-proBNP ≥82.45 pg/mL (highest quartile)	25.0 (0.6)	12.3 (0.8)	24.6 (0.9)	68.8 (1.2)	47.0
NT-proBNP ≥100 pg/mL	19.3 (0.6)	7.8 (0.6)	18.1 (0.9)	61.8 (1.4)	36.3
NT-proBNP ≥125 pg/mL	14.3 (0.5)	4.3 (0.4)	12.9 (0.7)	52.8 (1.5)	29.9
NT-proBNP ≥300 pg/mL	4.0 (0.2)	0.5 (0.2)	2.3 (0.3)	21.4 (1.2)	7.4
NT-proBNP ≥450 pg/mL	2.4 (0.2)	0.2 (0.1)	1.3 (0.2)	13.3 (0.9)	4.5

CVD indicates cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*The estimates are adjusted for the 2003 to 2004 US census population.

the lowest quartile. People with a history of CVD (median NT-proBNP, 168.5 pg/mL) had the higher risks of all-cause and cardiovascular mortality compared with people in the top quartile of NT-proBNP but without history of CVD (HRs were 0.78 [95% CI, 0.70–0.87] for overall mortality and 0.57 [95% CI, 0.48–0.68] for overall mortality in direct comparisons).

When modeled continuously, the associations of NT-proBNP with all-cause and cardiovascular mortality in people without a history of CVD were roughly linear (Figure 1; *P* values for test of nonlinearity >0.05). We observed similar associations of NT-proBNP with all-cause and cardiovascular mortality when the population was limited to people with a history of CVD, although the associations were less robust (shallower slope, lower HRs) (Figure 2).

Among individuals with elevated NT-proBNP defined using clinical cut points (ie, ≥300 or ≥450 pg/mL), the absolute and relative risks of cardiovascular and all-cause mortality were similar or higher to the risks observed among adults with a history of CVD (Table S1). For example, individuals with NT-proBNP ≥300 pg/mL (versus <300 pg/mL) were at a significantly elevated risk of cardiovascular mortality (HR, 2.47 [95% CI, 1.89–3.22]), similar to the risk in people with a history of CVD (HR, 2.70 [95% CI, 2.24–3.26]).

Older adults, Black adults, men, and those adults in the overweight and obese categories had higher incidence rates of all-cause mortality and cardiovascular mortality across NT-proBNP categories. Nonetheless, the relative associations (HRs) were similar across groups defined by sex, race and ethnicity and BMI, with no significant interactions: all *P* for interactions >0.05 (Figure 3). There was an interaction by age (*P*=0.02) for the mortality outcome; the effect of NT-proBNP was highest among those aged 45 to 64 years and above (Figure 3).

DISCUSSION

In a nationally representative sample of US adults, we found that adults without a history of CVD but who were in the top quartile of the distribution of NT-proBNP in the population had a strongly elevated risk of all-cause and cardiovascular mortality, even after adjustment for traditional cardiovascular risk factors. Individuals with high NT-proBNP levels (≥300 or ≥450 pg/mL) had risks of death that were similar or higher to adults with a self-reported history of CVD. The associations of NT-proBNP

Table 3. Rates (per 1000 Person-Years) and HRs of All-Cause and Cardiovascular Mortality According to Quartiles of NT-proBNP and History of CVD at Baseline, US Adults Aged ≥20 Years, NHANES 1999 to 2004

Variable	All-cause mortality			Cardiovascular mortality		
	Events	Incidence rate per 1000 person-years (95% CI)	HR (95% CI)*	Events	Incidence rate per 1000 person-years (95% CI)	HR (95% CI)*
NT-proBNP categories among adults with no history of CVD						
Quartile 1, <20.9 pg/mL	178	3.6 (3.0–4.4)	1 (Reference)	27	0.5 (0.3–0.9)	1 (Reference)
Quartile 2, 20.9–<42.4 pg/mL	268	4.9 (4.2–5.7)	1.08 (0.83–1.39)	73	1.3 (0.9–1.8)	1.89 (0.93–3.86)
Quartile 3, 42.4–<82.5 pg/mL	422	7.6 (6.8–8.7)	1.13 (0.93–1.38)	98	1.8 (1.4–2.3)	1.67 (0.89–3.14)
Quartile 4, ≥82.5 pg/mL	1406	23.8 (22.2–25.5)	1.67 (1.39–2.00)	438	6.9 (6.2–7.8)	2.87 (1.61–5.11)
CVD history	881	50.2 (46.2–54.6)	2.14 (1.75–2.61)	373	20.9 (18.3–23.8)	5.01 (2.77–9.06)

CVD indicates cardiovascular disease; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Adjusted for age, sex, race and ethnicity, body mass index, education, alcohol, smoking, physical activity, diabetes, hypercholesterolemia, hypertension, and estimated glomerular filtration rate.

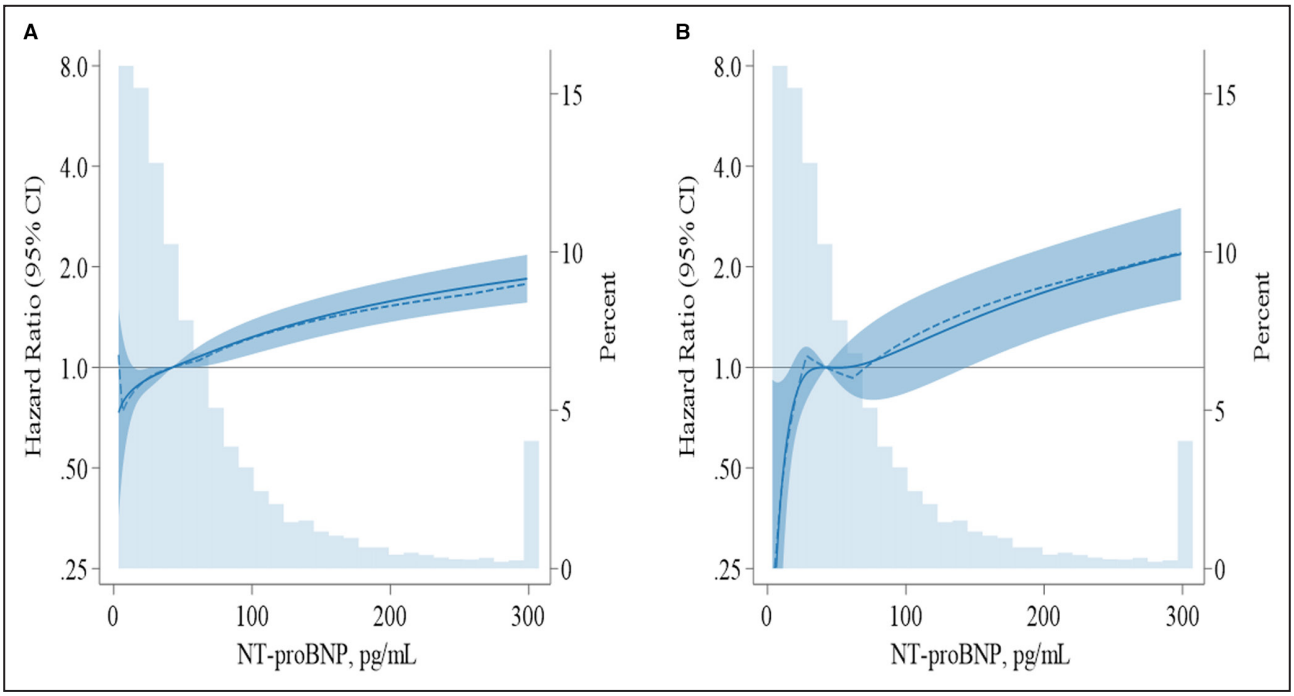

Figure 1. Hazard ratios (95% CIs) for the association of NT-proBNP (N-terminal pro-B-type natriuretic peptide) with all-cause (A) and cardiovascular (B) mortality among US adults without cardiovascular disease, National Health and Nutrition Examination Survey 1999 to 2004.

NT-proBNP was modeled using restricted cubic splines (solid line) and linear splines (dashed line). Knots were placed at 5th, 35th, 65th, and 95th percentiles. The models were centered at the median. The dark shaded areas are the 95% CIs for the restricted cubic spline. The light shaded area is the distribution (histogram) of NT-proBNP in the population. Models were truncated at the 1st (3.54 pg/mL) and 99th (811.9 pg/mL) percentiles of NT-proBNP. Plots were truncated at 300 pg/mL. The models were adjusted for age, sex, race, education, drinking, smoking, physical activity, body mass index, diabetes, hypertension, hypercholesterolemia, and chronic kidney disease. *P* value for nonlinearity was 0.076 for A and 0.289 for B.

with all-cause and cardiovascular mortality were continuous and graded, with similar relative risks across age, race and ethnicity, and BMI subgroups in the population. Our findings support the use of NT-proBNP for monitoring risk in the general population and suggest that NT-proBNP can be used to identify adults who may benefit from aggressive CVD prevention, which may include the use of proven cardioprotective therapies, such as statins.[25,26]

Elevated NT-proBNP was common in US adults without a history of CVD. Approximately 47.0 million adults are in the top quartile of NT-proBNP in the US population, 29.9 million have an NT-proBNP ≥125 pg/mL, and 7.4 million have NT-proBNP values of ≥300 pg/mL. Individuals with elevated NT-proBNP have a substantial excess risk of mortality, and those with the highest NT-proBNP levels, such as those with NT-proBNP of ≥300 pg/mL, had risks of all-cause and cardiovascular mortality that were higher than adults with a self-reported history of CVD. These results have implications for monitoring cardiovascular and mortality risk in the general US adult population.

Our findings are consistent with prior studies in community-based settings of middle-aged and older adults and provide strong evidence of the prognostic value of NT-proBNP in the general adult population.[5,8–12] Our study establishes national prevalence estimates of elevated NT-proBNP, extends previous studies of NT-proBNP and mortality to the general US population,[5,8–12] and demonstrates consistent associations of NT-proBNP with mortality across important population subgroups. NT-proBNP is strongly affected by several factors, including age, sex, BMI, and race and ethnicity. Age is strongly positively associated with NT-proBNP, with older adults having profoundly higher levels of NT-proBNP compared with younger individuals.[17,27] NT-proBNP is lower at higher levels of BMI thought to be related to excess adiposity.[18,28] Prior studies have also shown that NT-proBNP is lower in Black and Hispanic adults compared with White adults.[13,16] We show here that, although absolute values may differ across these important subgroups, the relative associations of NT-proBNP with all-cause and cardiovascular mortality were generally preserved across age, sex, race and ethnicity, and BMI.

The use of natriuretic peptide levels for diagnosis of decompensated heart failure in the clinical setting is

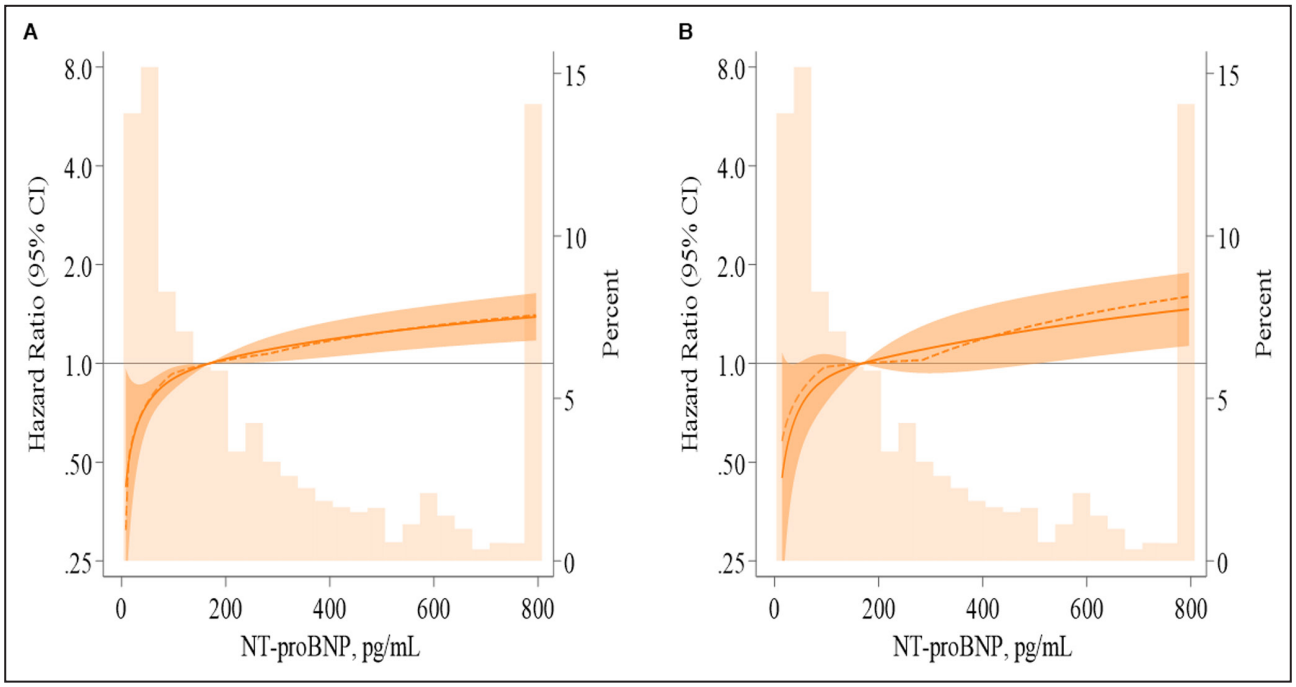

Figure 2. Hazard ratios (95% CIs) for the association of NT-proBNP (N-terminal pro-B-type natriuretic peptide) with all-cause (A) and cardiovascular (B) mortality among US adults with a history of cardiovascular disease, National Health and Nutrition Examination Survey 1999 to 2004.

NT-proBNP was modeled using restricted cubic splines (solid line) and linear splines (dashed line). Knots were placed at 5th, 35th, 65th, and 95th percentiles. The models were centered at the median. The dark shaded areas are the 95% CIs for the restricted cubic spline. The light shaded area is the distribution (histogram) of NT-proBNP in the population. Models were truncated at the 1st (7.9 pg/mL) and 99th (6849 pg/mL) percentiles of NT-proBNP. Plots were truncated at 800 pg/mL. The models were adjusted for age, sex, race, education, drinking, smoking, physical activity, body mass index, diabetes, hypertension, hypercholesterolemia, and chronic kidney disease. *P* value for nonlinearity was 0.415 for A and 0.632 for B.

well established,[3] and NT-proBNP is frequently used in patients suspected to have heart failure. Our study suggests that NT-proBNP has clinical prognostic value among those individuals without CVD, regardless of age, sex, race, ethnicity, or BMI. Nonetheless, the use of NT-proBNP for determining and monitoring risk in the general population is not considered standard clinical or public health practice.[12] Our findings inform the recently adopted universal definition and classification of heart failure, in which elevated NT-proBNP (≥125 pg/mL) is now used to define early nonsymptomatic or preclinical stage B heart failure,[29] a high-risk state. We demonstrated that in the general US adult population without a history of CVD, individuals with NT-proBNP levels of ≥125 pg/mL had a 2-fold increased risk of cardiovascular mortality, even after accounting for demographic and cardiovascular risk factors.

Several limitations of our study should be acknowledged. First, we only had a single NT-proBNP measurement, and we were unable to look at changes in NT-proBNP over time. Second, history of CVD was self-reported, which may be subject to misclassification. Self-reported CVD is known to be highly specific, but lacks sensitivity.[30,31] Third, our ability to examine mortality among subgroups was limited by the number of deaths, especially at younger ages. Fourth, we did not have information on cardiac function (ECG or echocardiogram), which limited our ability to assess the full extent of the association between NT-proBNP and subclinical cardiac health. Fifth, the ascertainment of cause of death was based exclusively on *ICD-10* codes. Finally, we did not have data on cardiovascular events.

The strengths of this study include the large, diverse, and nationally representative population. Our analysis also benefited from the rigorous and standardized measurements of traditional cardiovascular risk factors. We were able to examine both all-cause and cardiovascular mortality and generate the first national prevalence estimates of elevated NT-proBNP in the general US adult population. The interassay coefficients of variation for NT-proBNP were excellent, and this assay has been shown to be highly accurate and reliable in stored samples.[32]

In conclusion, elevated NT-proBNP is common in the general US adult population and is a powerful and independent risk factor for mortality. Our results

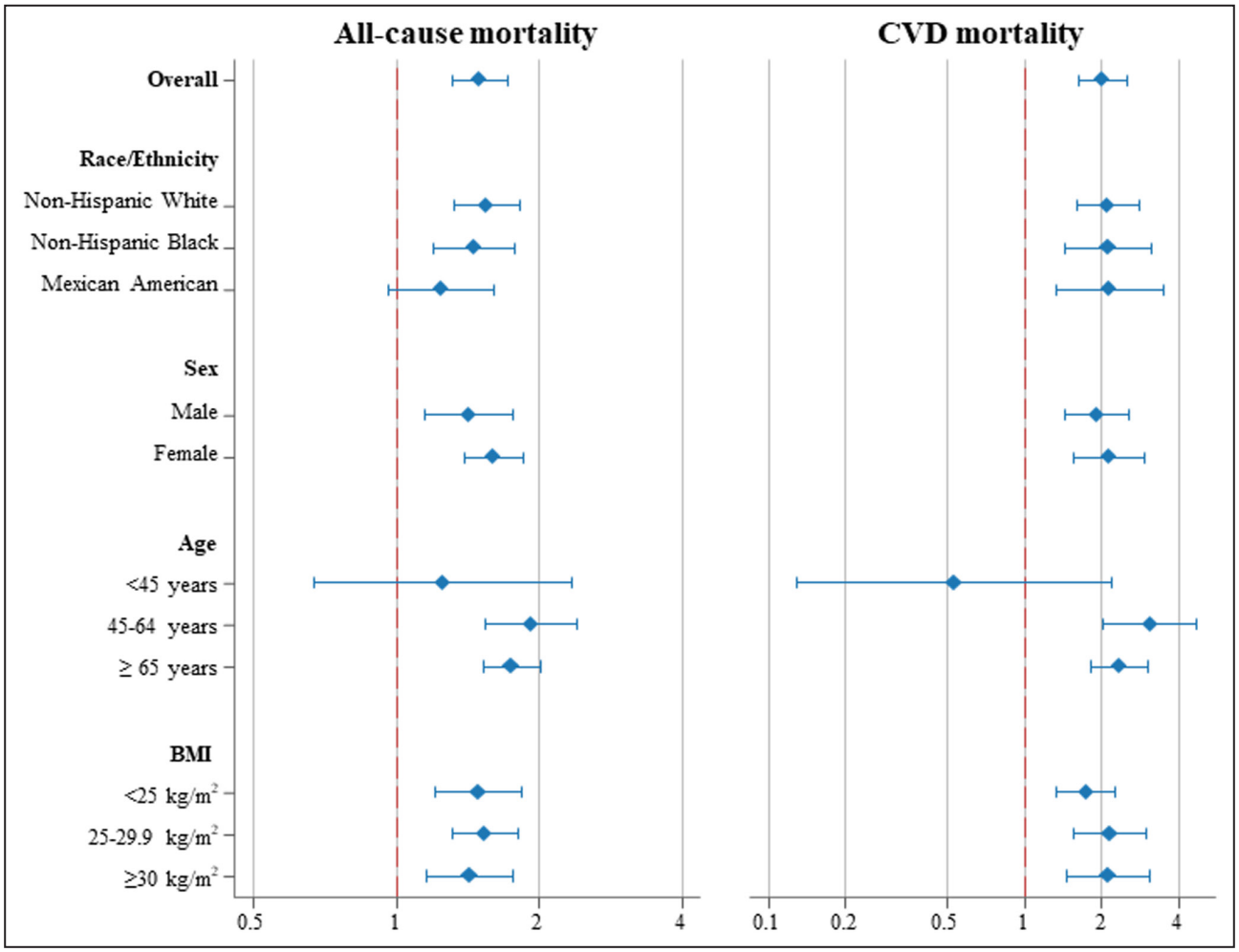

Figure 3. Adjusted hazard ratios (95% CIs) of NT-proBNP (N-terminal pro-B-type natriuretic peptide) (upper quartile [≥82.45pg/mL] vs other quartiles) among those without cardiovascular disease (CVD) or prior CVD association with all-cause mortality and cardiovascular mortality according to population subgroups, among US adults, National Health and Nutrition Examination Survey 1999 to 2004.
The estimates are adjusted for age, sex, race and ethnicity, body mass index (BMI), education, alcohol, smoking, physical activity, diabetes, high cholesterol, hypertension, and chronic kidney disease.

support the clinical use of NT-proBNP for monitoring risk and guiding primary prevention outside the setting of active clinical heart failure.

ARTICLE INFORMATION

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Disclosures

Dr. Christenson reports consulting for Siemens Healthineers, Roche Diagnostics, Roche Diagnostics, Sphingotech, and Quidel Medical.

Supplemental Material

Table S1
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Categories of NT-proBNP and risk of all-cause and cardiovascular mortality in US adults without cardiovascular disease, NHANES 1999-2004.

	Overall mortality			Cardiovascular mortality		
NT-proBNP categories	**Events**	**Incidence Rate per 1000 person-years (95% CI)**	**HR (95% CI) ***	**Events**	**Incidence Rate per 1000 person-years (95% CI)**	**HR (95% CI) ***
<75th percentile (<82.45 pg/mL)	868	5.4 (4.9, 5.9)	1 (Reference)	198	1.2 (1.0, 1.4)	1 (Reference)
≥75th percentile (≥82.45 pg/mL)	1406	23.8 (22.2, 25.5)	1.53 (1.35, 1.73)	438	6.9 (6.2, 7.8)	1.79 (1.40-2.27)
History of CVD	881	50.2 (46.2, 54.6)	1.96 (1.71, 2.25)	373	20.9 (18.3, 23.8)	3.12 (2.43-4.02)
<100 pg/mL	1026	5.9 (5.4, 6.4)	1 (Reference)	227	1.2 (1.1, 1.5)	1 (Reference)
≥100 pg/mL	1248	27.5 (25.5, 29.6)	1.49 (1.31, 1.69)	409	8.5 (7.6, 9.7)	1.98 (1.56, 2.51)
History of CVD	881	50.2 (46.2, 54.6)	1.88 (1.65, 2.13)	373	20.9 (18.3, 23.8)	3.21 (2.57, 4.02)
<125 pg/mL	1197	6.4 (5.9, 6.8)	1 (Reference)	269	1.4 (1.2, 1.6)	1 (Reference)
≥125 pg/mL	1077	32.9 (30.4, 35.6)	1.50 (1.31, 1.72)	367	10.6 (9.3, 12.1)	2.01 (1.61, 2.51)
History of CVD	881	50.2 (46.2, 54.6)	1.83 (1.60, 2.09)	373	20.9 (18.3, 23.8)	3.10 (2.52-3.83)
<300 pg/mL	1786	8.0 (7.6, 8.5)	1 (Reference)	448	1.9 (1.7, 2.1)	1 (Reference)
≥300 pg/mL	488	65.0 (57.8, 73.0)	1.73 (1.51, 1.99)	188	24.6 (20.5, 29.6)	2.47 (1.89, 3.22)
History of CVD	881	50.2 (46.2, 54.6)	1.69 (1.51, 1.89)	373	20.9 (18.3, 23.8)	2.70 (2.24, 3.26)
<450 pg/mL	1953	8.5 (8.0, 9.0)	1 (Reference)	506	2.0 (1.8, 2.3)	1 (Reference)
≥450 pg/mL	321	83.6 (73.3, 95.3)	1.86 (1.56, 2.22)	130	34.3 (28.1, 42.2)	2.82 (2.10, 3.79)
History of CVD	881	50.2 (46.2, 54.6)	1.64 (1.47, 1.84)	373	20.9 (18.3, 23.8)	2.59 (2.14, 3.13)

CVD: cardiovascular disease, HR: hazard ratio (95% confidence interval), IR: incident rate per 1000 person-years, *Model adjusts for age, sex, race/ethnicity, body mass index, education, alcohol, smoking, physical activity, diabetes, high cholesterol, hypertension, chronic kidney disease

Figure S1. Distribution of NT-pro-BNP among study participants overall and according to population subgroups (by age, sex, race/ethnicity, body mass index) among US adults, NHANES.